DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/21/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 1/22/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claim 39. Therefore, claims 18-20 and 33-39 are pending in the application.

Applicant's arguments filed on 7/21/09 have been fully considered but are not persuasive as explained below. The rejections below are pending/modified (due to claim amendments) or newly applied based upon the instant claim amendments.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional

application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The applications do not teach the instant combination of limitations: each strand is 18-27 nucleotides in length, wherein 18-23 are complementary to each other and at least 18 nucleotides of the antisense strand are complementary to a target; in combination with 10 or more pyrimidine nucleotides of each strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro; and in combination with the elements of the dependent claims.

Upon a review of 60/358,580, for example, the instant length limitations are disclosed on page 11 as being specific for the structures of Formula I, II, III, and IV; wherein the instant modification schematics are elements of other embodiments.

Although applicant points to support for the instant chemical modifications of claim 18 at page 30, lines 2-7 (as well as in the priority documents), these passage begins with "In another embodiment", and is not disclosed in combination with the instant size limitations or with the limitations of claims 19, 34, or 37.

Therefore, the instant claims are accorded the priority date of 1/14/04, which is the filing date of the instant application, as further explained in the new matter rejection below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-20 and 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation "10 or more pyrimidine nucleotides of the sense strand and antisense strand are chemically modified" in part d. However, the preceding portion of the claim does not require for each strand to comprise 10 or more pyrimidine nucleotides or is not closed to any specific sequence that has such. Therefore, there is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20 and 33-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 18 has been amended to require the combination of: each strand is 18-27 nucleotides in length, wherein 18-23 are complementary to each other and at least 18

nucleotides of the antisense strand are complementary to a target; in combination with 10 or more pyrimidine nucleotides of each strand being chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro; and in combination with the elements of the dependent claims.

Upon a review of the instant specification, support is not evident for this particular combination of elements.

Although applicant points to support for the instant chemical modifications of claim 18 at page 30, lines 2-7 (as well as in the priority documents), these passage begins with "In another embodiment", and is not disclosed in combination with the instant size limitations or with the limitations of claims 19, 34, or 37.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for the specific embodiment as instantly claimed.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 1/14/04, which is the filing date of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20 and 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record and as explained below.

It is noted that the references are of record and cited on the PTO-892 mailed on 12/21/06.

The invention of the above claims is drawn to a chemically modified double stranded nucleic acid comprising a sense strand and an antisense strand, wherein each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence, and the sense strand comprises a terminal cap moiety at the 5' and 3' end. The invention is further drawn to specific terminal cap moieties, as well as modifications to the duplex and a composition comprising the double stranded nucleic acid and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. (EMBO) teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications.

Elbashir et al. teach duplexes with 2 nt 3' overhangs, as well as blunt ended duplexes wherein all 21 nucleotides are complementary between the sense and antisense strand. Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach duplexes wherein the sense and antisense strands are complementary at 19 or 21 nucleotide positions (see for example, Figure 1D (1st duplex) and Figure 1F (1st duplex)). Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see page 6884). The 100% modified duplex taught by Elbashir et al. is considered to not comprise ribonucleotides.

Elbashir et al. do not teach double stranded nucleic acid molecules comprising the instantly recited terminal cap moieties and do not teach 2'-deoxy-2'-fluoro or phosphorothioate modifications. Elbashir et al. do not teach a composition comprising the double stranded nucleic acid molecule and a pharmaceutically acceptable carrier.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at

the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Matulic-Adamic et al. teach that preferred caps include 4', 5'-methylene nucleotides, 1-(beta-D-erythrofuranosyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, threo-pentofuranosyl nucleotides, acyclic 3', 4'-seco nucleotides, 3,4-dihydroxybutyl nucleotides, 3,5-dihydroxypentyl nucleotides, 3'-3'-inverted nucleotide moieties, 3'-3'-inverted abasic moieties, 3'-2'-inverted nucleotide moieties, 3'-2'-inverted abasic moieties, 5'-5'-inverted nucleotide moieties, and 5'-5'-inverted abasic moieties (see columns 3 and 4, for example). Matulic-Adamic et al. teach compositions comprising the nucleic acid and reaction buffer, which is a diluent.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with extensive modification with 2'-deoxy-2'-fluoro modifications, which resulted in successful RNA interference. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5).

Crooke teaches gapmer oligonucleotide chemistry and teaches that gapmer strategies increase oligonucleotide affinity to the target RNA (see column 9, for example). Crooke teaches chemical modifications that are incorporated to improve pharmacokinetic binding, absorption, distribution or clearance properties of the compound, affinity or specificity of the compound to target RNA, or modification of the charge of the compound (see column 7, for example).

Crooke teach that a particularly useful 2'-substituent group for increasing the binding affinity is the 2'-fluoro group (see column 12). Crooke also teaches 2'-O-methyl modifications.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics taught by Elbashir et al., wherein the molecule is formulated in a composition with a diluent, as taught by Matulic-Adamic et al. It would have been obvious to incorporate the specific modifications taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), wherein the molecule is formulated in a composition with a diluent, because Matulic-Adamic et al. teach successful inhibition of target gene expression with nucleic acid molecules formulated in a diluent. Furthermore, the reactions performed by Elbashir et al. require diluents such as buffers and water.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), with the modifications taught by Parrish

et al. and Matulic-Adamic et al. because each of the modifications were known in the art to protect nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules, as taught by Matulic-Adamic et al. Additionally, Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of long dsRNA and ribozymes, respectively, with successful inhibition of target gene expression.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters delivery problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Crooke teaches that gapmer oligonucleotide chemistry has provided antisense oligonucleotides with increased target affinity and pharmacokinetic properties. Crooke teaches that different modifications at different regions of the

oligonucleotide have been tested in order to optimize oligonucleotide activity. Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Crooke is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations (i.e. regions/positions of duplex or pyrimidine v. purine) and amounts, as taught by Crooke, into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes, as

evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in RNA interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications

at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

Applicant argues that the instant claims are directed to nucleic acid molecules with extensive modifications at specific positions and specific types of nucleotides. It is noted that the only position specific modification that is instantly claimed are terminal caps, which by nature are located in terminal positions. It was known and routine in the art to incorporate terminal cap moieties into nucleic acid inhibitory molecules, as set forth in the instant rejection. Regarding types of nucleotides, there is a finite number of choices for the modifications of the prior art to be incorporated at, purines or pyrimidines. It is certainly within the realm of routine optimization/design choice to

incorporate the modifications at a purine or a pyrimidine, given that there are only two choices. Furthermore, the claims are not directed to any specific pattern of modification that has demonstrated any unexpected property, given that the claims embrace combinations of modifications at different positions depending on the target sequence. The quantity of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

As evidenced by Matulic-Adamic et al. and Parrish et al., it was known to incorporate extensive modification into nucleic acid inhibitory molecules, wherein the molecules of Parrish et al. act via RNAi.

Applicant continues to argue the interpretation of the Elbashir et al. reference. Again, it is noted that the only modification schematic that is taught away by Elbashir et al. is 100% modification of one or both strands with one type of modification, either 2'-deoxy or 2'-O-methyl. This does not teach away from incorporation of any other type or combination of modifications and does not teach away from 2'-O-methyl or 2'-deoxy modifications at any other percentages. It is believed that applicant's arguments directed to Elbashir et al. have been addressed in detail. Given that Elbashir et al. is evidence that there is a need to balance stability and activity via incorporating different levels of modification, one would have been motivated to combine the modifications at varying positions, which was not done by Elbashir et al.

Each of the chemical modifications were known in the nucleic acid inhibitor art to impart beneficial stability properties to such nucleic acid inhibitors. Furthermore, it was known in the art that testing/optimization is needed to determine optimal configurations

of the modifications within the inhibitory molecules, as evidenced by Elbashir et al. and Crooke. Although applicant asserts that the examiner has cherry picked the modifications from the art, each of the modifications are equally obvious in view of the teachings of the prior art. Furthermore, applicant is not claiming any specific configuration of any specific modifications, but is rather claiming a huge genus of combinations of possible chemical modifications and schematics thereof that are target sequence specific for the positions.

Elbashir et al. is evidence that incorporation of such chemical modifications into siRNA molecules results in active molecules in some configurations and inactive molecules in others, supporting that routine optimization is needed. Furthermore, Elbashir et al. is evidence that modification is well tolerated in the terminal portions of the duplex, offering further motivation to modify the terminal regions. Elbashir et al. teaches that some modification does not affect RNAi, but helps to reduce the cost of RNA synthesis and may enhance RNase resistance of siRNA duplexes (see page 6885, column 1). Applicant argues that Elbashir only succeeded at modifying a single terminal region on each strand. Importantly, this is all that Elbashir et al. tested and therefore does not teach away from incorporating terminal modifications at the other end. Since the modifications were tolerated on the one end, one would have been motivated to incorporate them on the other end. Again, applicant is not claiming any specific configuration of modifications, but is rather claiming a genus of modification types or combinations thereof at various positions depending on the target sequence.

In addition to Elbashir et al., Crooke is evidence that it was routine in the nucleic acid inhibitor art to incorporate the chemical modifications in different patterns to result in active molecules with improved stability. Therefore, it was known in the art that there must be a balance between improving stability and maintaining a level of activity. Simply because the examiner has set forth that the motivation to incorporate the known modifications is to improve stability does not mean that activity is not a consideration in the routine optimization of placing such modifications. The examiner has not asserted that such modifications should be freely and without limitation incorporated, but rather that it would have been obvious to incorporate the modifications with the motivation of enhancing stability, although it is recognized that optimization is needed to result in active molecules.

Applicant argues that Parrish et al. teaches that some modifications resulted in instability whereas others were compatible, depending on the location and extent to which the modification was applied, which is again supportive of the instant position that routine optimization is needed to determine the optimal configuration for the instant modifications. Parrish et al. teaches extensive modification of a long dsRNA with 2'-deoxy pyrimidine modifications with resultant interference activity. It is noted that the dsRNA molecules of Parrish et al. were extensively modified and resulted in strong RNAi activity. Applicant argues that Parrish et al. is silent as to incorporation into cytidines, which is not an element of the instant claims. Furthermore, the claims do not require any specific level of activity, so applicant's arguments regarding a decrease in activity reported by Parrish et al. for a specific embodiment is not directed to an element

of the instant claims. Chemical modifications are often incorporated in the art by preference even if they result in a decrease in activity for the benefit of increasing stability. The balance of these two properties is the element that is routine optimization. Although applicant argues a limitation that is not required by the instant claims, Parrish et al. does teach extensive pyrimidine modification with strong RNAi activity (see Figure 5 on page 1081), thus offering motivation to extensively modify at various positions.

Applicant argues the teachings of Parrish et al. regarding phosphorothioate modifications and points to page 1084. Clarification is requested because the statement by applicant is not evident upon a review of the document and particularly at page 1084. Simply because Parrish et al. teach that the antisense strand is more sensitive than the sense strand does not mean that Parrish et al. teaches away from the incorporation of known chemical modifications in different combinations and locations to optimize the activity/stability balance.

Applicant argues that Crooke teaches gapmer patterns, never venturing beyond a single type of modification, 2'-O-methyl, although Crooke clearly had knowledge of a vast number of stabilizing modifications. Crooke is not required to test every possible modification that is known in the art to add stability to nucleic acid molecules to be evidence that it was known in the art to incorporate chemical modifications to enhance stability of nucleic acid inhibitory molecules and that optimization is needed to result in balance between enhancing stability and retaining activity.

Applicant points out that Crooke teaches that it is important not only to pick the right modification(s), but also to position the modifications at the right place because

otherwise the molecule would be inactive. This is completely consistent with the position of the examiner that it was known in the art that optimization of placement/configuration of the modifications is needed and within the grasp of the skilled artisan. In the case of Elbashir et al., Elbashir et al. is silent as to modifications between the 3' terminal regions and the fully modified schematic, wherein fully modified duplexes with 2'-deoxy or 2'-O-methyl modifications abolished activity, supporting again that optimization is needed to determine placement of such modifications for active molecules.

Applicant points to *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by Elbashir et al. and Crooke.

In view of *KSR International Co. v. Teleflex Inc.*, when a combination of admittedly old elements produces a new and beneficial result never attained before, it is

evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.

The mere selection of elements from various prior art references and combining them together with no new function is an obvious use of common sense by one skilled in the art and therefore not patentable.

Furthermore, Elbashir et al. offers motivation to modify terminal nucleotides and Matulic-Adamic et al. teaches the benefit of a plethora of terminal cap moieties and teaches incorporation of such moieties at 5' and/or 3' ends. It is certainly within the realm of routine optimization to incorporate the terminal cap moieties at one or both of the 5' and 3' ends on each of the strands, as a double stranded nucleic acid molecule only has four possible ends to modify. Additionally, the instant claims do not exclude modification at all four ends but rather only requires the 5' and 3' end of the sense strand. Within instant scope, one would certainly expect for routine optimization to result in active molecules.

One of skill in the art would reasonably expect for the modifications of Matulic-Adamic et al. to likely benefit the molecules of Elbashir et al. as well. As explained above, the motivation need not be the same motivation set forth by applicant, but rather the motivation to enhance the stability of the molecules as set forth by Matulic-Adamic et al. Elbashir et al. teaches that preferred molecules are modified in the 3' terminal

regions. Therefore, one would reasonably expect for the terminal cap moieties of Matulic-Adamic et al. to enhance the stability of the molecules of Elbashir et al. as well.

Applicant points to specific species within the instant genus in the instant specification and compares the molecules to those of Elbashir et al. Again, the instant genus is huge depending on the target sequence and combination/quantity of each type of the instants modifications. Armed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules. The unmet need, as required by KSR, is that of balancing stability and activity with known chemical modifications.

Giese et al. (US 2004/0180351 A1) is not relied upon as a reference in the instant rejection, but is relied upon for additional response to applicant's arguments given the effective filing date of the instant claims as set forth above.

Giese et al. teach siRNA molecules comprising a sense and an antisense strand, comprising a sense region and an antisense region, respectively, wherein the antisense region is complementary with the mRNA of a target gene and is complementary with the sense region.

Giese et al. teach that in addition to the various modifications or designs of the inventive RNAi molecules, further or additional modification of the nucleotides may include the use of a phosphorothioate backbone of the RNAi molecules which may be

either complete or partial in order to inhibit endonuclease function (see paragraph [0170]).

Giese et al. teach that 2'-O-alkyl modifications stabilize RNAi molecules against degradation, but to a certain degree this is counterbalanced by the effect that 2'-alkyl modifications generally result in a reduced knockdown activity. Therefore, Giese et al. offers motivation to incorporate 2'-O-alkyl modifications in specific locations, rather than to blanket the siRNA with such modifications, consistent with the teachings of Elbashir et al. Giese et al. offers motivation to incorporate such modifications in a manner that is minimal enough to not reduce knockdown activity. Giese et al. teach that accordingly, the design of RNAi molecules has to balance stability against activity (see paragraph [0176]). Giese et al. teach that the most efficient molecules were modified at alternating positions of both strands.

Giese teaches incorporation of various 2'-position modifications including amino, fluoro, methoxy, alkoxy, and alkyl (see paragraph [0024]). Giese teaches siRNA molecules wherein each strand comprises a plurality of groups of modified nucleotides having a modification at the 2'-position whereby each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides, wherein the flanking group is either unmodified or is modified with a different modification than the modified groups (see paragraph [0025]).

Giese et al. teach siRNAs with various end modifications on the sense and antisense strand and particularly teach the sense strand should be modified at the 5' end to reduce off-target effects mediated by an otherwise functional sense strand which

results in increased specificity of the siRNA which is advantageous for any medical use of the RNAi molecules or any target validation using the siRNA (see paragraphs 0103 and 0173).

Therefore, Giese et al. is further evidence that combining modifications in regions, including the instant types of chemical modifications is a matter of routine optimization of the balance of stability/activity, and that this is a better approach than blanketing the molecule with one type of modification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-20 and 33-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-50 of copending Application No. 10/923,536. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to chemically modified double stranded nucleic acid molecules with overlapping structural characteristics and modifications. The instant molecules are not designed to be targeted to any specific target RNA sequence and are therefore obvious in view of the claims of application '536 that recite molecules with overlapping structural characteristics.

Application '536 recites double stranded nucleic acid molecules that comprise a sense and an antisense strand, wherein the antisense region is about 16 to about 25 nucleotides and the sense region is about 3 to about 15 nucleotides in length. Application '536 recites 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, and LNA modifications at varying amounts in one or both strands, as well as terminal cap moieties including inverted deoxy abasic moieties. Application '536 recites terminal cap moieties at the 5'-end, 3'-end or both ends of the sense strand and the 3' end of the antisense strand. Application '536 recites a composition comprising the nucleic acid molecule in a pharmaceutically acceptable carrier or diluent. Therefore, the instant claims are obvious in view of the claims of application '536.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests that this rejection be held in abeyance until such time when it becomes the sole remaining rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
Art Unit 1635

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